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PAGE 02/04

In re:

Serial #: 09/756,688
For: Removable Bearing Assemblies
Filed: January 9, 2001
Inventor: Richard L. Fisher
GAU: 3617
Examiner: Avila
Docket #: Fisher-001221
Publication #: US-2001-0031586-A1

DECLARATION OF BRIAN BELL

I, Brian Bell, declare as follows:

1. I am a citizen of the United States and reside at 2378 Wildlife Court, Richfield, WI, 53076.
2. I have been employed by Cedar Lake Sales for approximately 15 years. Cedar Lake Sales has been in the business of selling marine mud motors or motors for mud boats to consumers for approximately 5 years. Cedar Lake Sales also provides maintenance and repair services for marine mud motors or motors for mud boats, and has been providing such maintenance and repair services for approximately 5 years. *(Cedar Lake Sales has been in business 30 years)*
3. I have been involved in the purchase and sales and service of such marine mud motors or motors for mud boats for approximately 5 years. Over the years I have sold and serviced hundreds of mud motors, a.k.a motors for mud boats, as well as discussed these motors with owners, operators, salespeople and manufacturers of such motors.
4. Those of ordinary skill in the art, including myself, recognize the words "marine mud

Page 1

02/25/2004 09:49 3203638443

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PAGE 03/04

motor" as accurately and interchangeably describing the marine propulsion system 100 illustrated in figure 1 of the above referenced pending patent application.

5. Those of ordinary skill in the art, including myself, recognize the words "elongate drive tube" as accurately and interchangeably describing the casing 140 illustrated in figure 1 of the above referenced pending patent application.
6. Those of ordinary skill in the art, including myself, recognize the words "drive shaft" as accurately and interchangeably describing the propeller shaft 130 illustrated in figure 1 of the above referenced pending patent application.
7. Those of ordinary skill in the art, including myself, recognize the words "drive assembly housing" as accurately and interchangeably describing the bearing housing 210 illustrated in figure 2 of the above referenced pending patent application.
8. Those of ordinary skill in the art, including myself, recognize the words "seal cap" as accurately and interchangeably describing the cover 220 illustrated in figure 2 of the above referenced pending patent application.
9. Those of ordinary skill in the art, including myself, recognize the words "drive assembly" as accurately and interchangeably describing the sealed bearing unit 200 illustrated in figure 1 of the above referenced pending patent application.
10. Those of ordinary skill in the art, including myself, recognize the words "a bearing in rotational communication *between* the drive assembly housing and the drive shaft" do not require that the bearing be in rotational communication solely with the drive assembly housing. The location and operation of bearings 260 - 264 as illustrated in the figures of the above referenced pending patent application are recognized as being in rotational communication *between* the drive assembly housing and drive shaft to those of ordinary

Page 2

02/25/2004 09:49 3203638443

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PAGE 04/04

skill in the art, and one skilled in the art would be able to recognize the identity and be enabled.

11. Those of ordinary skill in the art, including myself, recognize the words "a seal contained within the drive assembly housing, configured to restrict contaminants from entering the drive assembly housing" as accurately and interchangeably describing the description in the above referenced pending patent application of water being prevented from entering, and that in fact water is a contaminant and is recognized and understood by those of ordinary skill in the art as not only being a contaminant, but also being the vehicle through which additional contaminants are transported.

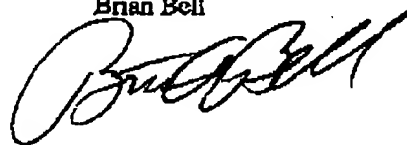
I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize that validity of the application or any patent issuing thereon.

Dated: February _____, 2004

March 3

Signed:

Brian Bell



Page 3

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PAGE 11/13
PAGE 02
PAGE 02/13

In re:

Serial #: 09/756,688
For: Removable Bearing Assemblies
Filed: January 9, 2001
Inventor: Richard L. Fisher
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Examiner: Avila
Docket #: Fisher-001221
Publication #: US-2001-0031586-A1

DECLARATION OF ROCK CRAWFORD

I, Rock Crawford, declare as follows:

- 1. I am a citizen of the United States and reside at 11923 West 800 North, Monticello, IN, 47960.**
- 2. I have been employed by Pearson's Marina since 1998. Pearson's Marina has been in the business of selling marine mud motors or motors for mud boats to consumers for approximately 2 years. Pearson's Marina also provides maintenance and repair services for marine mud motors or motors for mud boats, and has been providing such maintenance and repair services for approximately 2 years.**
- 3. I have been involved in the purchase and sales and service of such marine mud motors or motors for mud boats for approximately 2 years. Over the years I have sold and serviced thousand of boats and motors, including mud boats and motors, a.k.a motors for mud boats, as well as discussed these motors with owners, operators, salespeople and manufacturers of such motors.**

4. Those of ordinary skill in the art, including myself, recognize the words "marine mud motor" as accurately and interchangeably describing the marine propulsion system 100 illustrated in figure 1 of the above referenced pending patent application.
5. Those of ordinary skill in the art, including myself, recognize the words "elongate drive tube" as accurately and interchangeably describing the casing 140 illustrated in figure 1 of the above referenced pending patent application.
6. Those of ordinary skill in the art, including myself, recognize the words "drive shaft" as accurately and interchangeably describing the propeller shaft 130 illustrated in figure 1 of the above referenced pending patent application.
7. Those of ordinary skill in the art, including myself, recognize the words "drive assembly housing" as accurately and interchangeably describing the bearing housing 210 illustrated in figure 2 of the above referenced pending patent application.
8. Those of ordinary skill in the art, including myself, recognize the words "seal cap" as accurately and interchangeably describing the cover 220 illustrated in figure 2 of the above referenced pending patent application.
9. Those of ordinary skill in the art, including myself, recognize the words "drive assembly" as accurately and interchangeably describing the sealed bearing unit 200 illustrated in figure 1 of the above referenced pending patent application.
10. Those of ordinary skill in the art, including myself, recognize the words "a bearing in rotational communication ~~between~~ the drive assembly housing and the drive shaft" do not require that the bearing be in rotational communication solely with the drive assembly housing. The location and operation of bearings 260 - 264 as illustrated in the figures of the above referenced pending patent application are recognized as being in rotational

communication ~~between~~ the drive assembly housing and drive shaft to those of ordinary skill in the art, and one skilled in the art would be able to recognize the identity and be enabled.

11. Those of ordinary skill in the art, including myself, recognize the words "a seal contained within the drive assembly housing, configured to restrict contaminants from entering the drive assembly housing" as accurately and interchangeably describing the description in the above referenced pending patent application of water being prevented from entering, and that in fact water is a contaminant and is recognized and understood by those of ordinary skill in the art as not only being a contaminant, but also being the vehicle through which additional contaminants are transported.

I heroby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize that validity of the application or any patent issuing thereon.

Dated: February 25, 2004

Signed: 
Rock Crawford

(13 pgs total)

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office
on the date shown below.

Albert W. Watkins

Type or print name of person signing certification

March 22, 2004

Signature

Date

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In re:

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For: Removable Bearing Assemblies
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Inventor: Richard L. Fisher
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DECLARATIONS IN ACCORD WITH 37 CFR 1.195 AND MPEP 1207

In the outstanding action, the Examiner states on page 5 in lines 4 - 5 that "the statements in the affidavits are self serving statements." While this is certainly the case, the appellant and his representative do not believe such statements, whether self serving or otherwise, should be disregarded. Such would fly in the face of affidavit practice as it exists before the Patent Office. Nevertheless, appellant is providing herewith an additional set of declarations made by two individuals very experienced in the marine industry and familiar with the terminology used therein. These individuals recognize the same identity recognized by the appellant. These declarations were not earlier forwarded because the Examiner first objected to the declarations by the appellant and his partner as being self-serving. Consequently, consideration of these in the present appeal is respectfully requested, and appropriate.

A supplemental declaration by the appellant is similarly provided herewith, which restates the contents of the previous declaration but which further sets forth the appellant's experience in this

field. Since the content herein does not differ, but merely establishes the basis for the credibility of the appellant which has been questioned in the last office action, entry of the same is similarly requested and appropriate.

These affidavits are being submitted by facsimile, while the appeal brief is being submitted simultaneously but under separate cover, and by mail.

Sincerely,



Albert W. Watkins

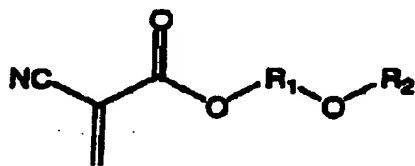
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Examples of preferred alkyl ester cyanoacrylates include, but are not limited to, butyl lactoyl cyanoacrylate (BLCA), butyl glycoloyl cyanoacrylate (BGCA), isopropyl glycoloyl cyanoacrylate (IPGCA), ethyl lactoyl cyanoacrylate (ELCA), and ethyl glycoloyl cyanoacrylate (EGCA). BLCA may be represented by formula (I) above, wherein R₁ is H, R₂ is methyl and R₃ is butyl. BGCA may be represented by formula (I) above, wherein R₁ is H, R₂ is H and R₃ is butyl. IPGCA may be represented by formula (I) above, wherein R₁ is H, R₂ is H and R₃ is isopropyl. ELCA may be represented by formula (I) above, wherein R₁ is H, R₂ is methyl and R₃ is ethyl. EGCA may be represented by formula (I) above, wherein R₁ is H, R₂ is H and R₃ is ethyl. Other cyanoacrylates useful in the present invention are disclosed in U.S. Patent No. 3,995,641 to Kronenthal et al., the entire disclosure of which is hereby incorporated by reference.

Alternatively, or in addition, the present invention provides for the use of alkyl ether cyanoacrylate monomers. Alkyl ether cyanoacrylates have the general formula:



(II)

where R₁ is a straight, branched or cyclic alkyl, and R₂ is a straight, branched or cyclic alkyl group. Preferably, R₁ is a C₁, C₂ or C₃ alkyl group, such as methyl or ethyl; and R₂ is a C₁-C₁₆ alkyl group, more preferably a C₁-C₁₀ alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl, octyl, nonyl or decyl, and even more preferably a C₂, C₃ or C₄ alkyl group.

Examples of preferred alkyl ether cyanoacrylates include, but are not limited to, isopropoxy ethyl cyanoacrylate (IPECA) and methoxy butyl cyanoacrylate (MBCA). IPECA may be represented by formula (II) above, wherein R₁ is ethylene and R₂ is isopropyl. MBCA may be represented by formula (II) above, wherein R₁ is n-butylene and R₂ is methyl.

Alkyl ester and alkyl ether cyanoacrylates are particularly useful for medical applications because of their absorbability by living tissue and associated fluids. According to the present invention, 100% of the polymerized and applied cyanoacrylate may be absorbed in a period of less than 2 years, such as approximately 2-24 months after application of the adhesive to living tissue. Alternatively, the absorption rate can be tailored to provide absorption rates of, for example, 3-18 months, including 3-6

months, 6-12 months, or 12-18 months. Of course, the present invention is not particularly limited to any absorption time, as the desired absorption time can vary depending on the particular uses and tissues involved. Thus, for example, longer absorption time may be desired where the adhesive composition is applied to hard tissues, such as bone, but a faster absorption time may be desired where the adhesive composition is applied to softer tissues.

The selection of monomer will affect the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. Two or more different monomers that have varied absorption and/or polymerization rates may be used in combination to give a greater degree of control over the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. Thus, an important aspect of embodiments of the invention lies in the selection of the monomer and initiator to control within relatively narrow and predictable ranges both the polymerization and absorption rates.

According to embodiments of the present invention, the adhesive composition comprises a mixture of monomer species, where one monomer species is absorbable and the other monomer species is non-absorbable, or where both monomers are absorbable but one monomer species has a faster absorption or degradation rate than the other monomer species. Where two monomer species having different absorption rates are used, it is preferred that the absorption rates be sufficiently different that a mixture of the two monomers can yield a third absorption rate that is effectively different from the absorption rates of the two monomers individually. Thus, for example, it is preferred that the absorption rate of the faster absorbing monomer species be at least 10% faster than the absorption rate of the slower absorbing monomer species. More preferably, the absorption rate of the faster absorbing monomer species be at least 25% or 50% faster, or even 75% or 100% faster, than the absorption rate of the slower absorbing monomer species. Preferably, according to embodiments, the absorbable or faster absorbing/degrading monomer species is an alkyl ester cyanoacrylate or alkyl ether cyanoacrylate, while the non-absorbable or slower absorbing/degrading monomer species is not an alkyl ester cyanoacrylate or alkyl ether cyanoacrylate. The non-absorbable or slower absorbing/degrading monomer species can be, for example, any suitable and biocompatible monomer species, such as a 1,1-disubstituted ethylene monomer including but not limited to cyanoacrylates such as alkyl alpha-cyanoacrylates.

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More particularly, the non-absorbable or slower absorbing/degrading monomer species is a polymerizable monomer that is readily polymerizable, e.g. anionically polymerizable or free radical polymerizable, or polymerizable by zwitterions or ion pairs to form a polymer. Such monomers are disclosed in, for example, U.S. Patents

5 Nos. 5,328,687 and 5,928,611 to Leung et al., U.S. Patent Application Serial No. 09/430,177, filed on October 29, 1999, and U.S. Patent Application Serial No. 09/471,392 filed December 23, 1999, which are hereby incorporated in their entirety by reference herein. Preferred monomers include 1,1-disubstituted ethylene monomers, such as α -cyanoacrylates including, but not limited to, alkyl α -cyanoacrylates having
10 an alkyl chain length of from about 1 to about 20 carbon atoms or more, preferably from about 2 to about 12 or more, and more preferably from about 3 to 8 carbon atoms. Examples of such suitable monomers thus include, but are not limited to, alkyl α -cyanoacrylates such as octyl (such as 2-octyl), hexyl, and butyl α -cyanoacrylates.

In embodiments, the respective monomer species can be mixed in any suitable
15 ratio to provide the desired degradation rate of the final polymer material. Thus, for example, suitable mixing ratios can range anywhere from about 1:99 or from about 10:90 to about 90:10 or about 99:1 in terms of parts by weight faster absorbing monomer to parts by weight non-absorbable or slower absorbing monomer. Preferred ratios are from about 15:85 to about 85:15 or from about 25:75 to about 75:25. For
20 example, a desired degradation rate can be obtained by mixing faster absorbing monomer species and non-absorbable or slower absorbing monomer species in a weight ratio of about 50:50. In embodiments, a suitable composition can be obtained by mixing faster absorbing monomer species and non-absorbable or slower absorbing monomer species in a weight ratio of from about 40:60 to about 60:40. These ratios are
25 particularly beneficial for achieving a desired balance between the relatively fast degradation rates of alkyl ester cyanoacrylates and the relatively slow degradation rates of other monomer species such as alkyl alpha-cyanoacrylates. However, these ratios and the present invention are in no way limited to such combinations.

For example, suitable compositions according to the present invention can be
30 prepared by mixing suitable quantities of 2-octyl alpha-cyanoacrylate with one of butyl lactoyl cyanoacrylate (BLCA), butyl glycoloyl cyanoacrylate (BGCA), isopropyl glycoloyl cyanoacrylate (IPGCA), ethyl lactoyl cyanoacrylate (ELCA), and ethyl

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glycoloyl cyanoacrylate (EGCA). Preferably, such mixtures range from ratios of about 75:25 to about 25:75 by weight such as from about 60:40 to about 40:60 by weight.

In addition, although the above discussion is with respect to a composition containing only two different monomer species, the present invention is not limited to such an embodiment. Rather, as desired, the monomer composition can have two or more different monomer species, to provide further control over the absorption/degradation rate and other characteristics of the resultant polymer. Thus, for example, the composition can include two, three, four, five or even more different monomer species. Furthermore, where more than two monomer species are used, the various monomer species need not all have different absorption/degradation rates, although it is preferred that the monomer species individually provide at least two different absorption/degradation rates.

Some alkyl ester cyanoacrylate monomers may react slowly due to bulky alkyl groups, apparently limiting their applicability as surgical adhesives. By themselves, alkyl ester cyanoacrylates cure in several hours, or in some cases do not fully cure at all. To overcome problems associated with slow polymerization of the monomers, a compatible agent which initiates or accelerates polymerization of the alkyl ester cyanoacrylate monomer, may be used with the monomer composition. Initiators and accelerators particularly suitable for use with alkyl ester cyanoacrylates provide a fast cure rate while retaining the absorbable properties of the adhesive. Alkyl ester cyanoacrylates stimulated to cure by a suitable initiator or accelerator may be made to cure in as short as a few seconds to a few minutes. The cure rate may be closely controlled by selection of an amount or concentration of initiator or accelerator added to the cyanoacrylate and may thus be readily controlled by one skilled in the art in light of the present disclosure. A suitable initiator provides a consistent controllable complete polymerization of the monomer so that the polymerization of the monomer can be made to occur in the time desired for the particular application. Quaternary amine initiators or accelerators are particularly desirable with alkyl ester cyanoacrylate monomers for such reasons.

The initiator or accelerator may be in the form of a solid, such as a powder or a solid film, or in the form of a liquid, such as a viscous or paste-like material. The initiator or accelerator may also include a variety of additives, such as surfactants or emulsifiers. Preferably, the initiator or accelerator is soluble in the monomer composition, and/or comprises or is accompanied by at least one surfactant which, in

embodiments, helps the initiator or accelerator co-elute with the monomer composition. In embodiments, the surfactant may help disperse the initiator or accelerator in the monomer composition.

5 The initiator or accelerator may be applied to tissue before the monomer composition, or may be applied directly to the monomer composition once the monomer composition is applied to tissue. In embodiments, the initiator or accelerator may be combined with the monomer composition just prior to applying the composition to tissue.

10 The selection of an initiator or accelerator may additionally affect the rate at which the polymerized monomer is absorbed by living tissue. Therefore, the most suitable initiators or accelerators are those that polymerize the monomer at a rate suitable for medical applications while providing a polymer that is substantially absorbed in less than two years. For the purposes of this invention, the phrase "suitable for medical application(s)" means that the initiator or accelerator polymerizes the
15 monomer in less than 5 minutes or less than 3 minutes, preferably in less than 2.5 minutes, more preferably in less than 1 minute, and often in less than 45 seconds. Of course, the desired polymerization time can vary for different compositions and/or uses. Preferably, a suitable initiator or accelerator and a suitable monomer are selected to provide a polymer that is substantially absorbed by a living organism in 2-24 months, such as 3-18 months or 6-12 months after application of the adhesive to living tissue.
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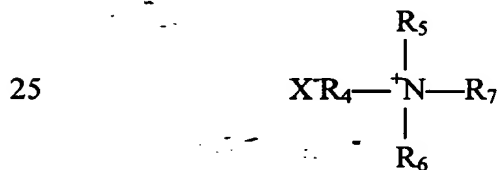
The present invention provides a method of treating living tissue, where a selected absorption rate of the polymer can be provided by selecting an alkyl ester cyanoacrylate monomer for treatment of the tissue; selecting a suitable polymerization initiator or accelerator for the monomer on the basis of the desired absorption rate; and
25 applying to living tissue the polymerization initiator or accelerator and said monomer to form an absorbable adhesive polymer. A suitable initiator or accelerator in a suitable quantity can be selected in light of the present disclosure, in combination with the selection of monomer, to produce a polymer with a desired absorption rate. A screening process utilizing routine experimentation may be used to identify combinations of
30 monomers and initiators or accelerators that possess the desired reaction kinetics and produce a polymer that is absorbed *in vivo* in the desired period of time. Particularly beneficial initiators or accelerators, as well as monomers, are identified by the present disclosure. Therefore, for example, a butyl lactoyl cyanoacrylate monomer may be polymerized with, for example, domiphen bromide to test the polymerization rate. The

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quantity, or type, of initiator or accelerator or monomer may be adjusted if the desired polymerization rate is not achieved. Further, the polymer may be tested by *in vivo* application on animal (including human) tissue to determine absorption rates.

Depending, for example, on the necessary healing time for a wound, a
 5 corresponding absorption rate may be desired. Since healing times vary in different organisms and different tissues, the ability to control the absorption rate of the adhesive is beneficial to ensure that the adhesive polymer lasts long enough to provide time for the wound to heal, but absorbs within a reasonable time, preferably within 2 years from application of the adhesive to living tissue. Thus, according to the present invention, the
 10 absorption rate of the adhesive material can be selected in one of several ways. First, the absorption rate can be selected by determining desired specific monomer and initiator species. Thus, for example, where an alkyl ester cyanoacrylate is used as the monomer, the absorption rate can be selected by proper selection of a desired initiator or accelerator, such as a quaternary amine polymerization initiator or accelerator. In other
 15 embodiments, for example where a mixture of monomer species is used, such as where a faster absorbing alkyl ester cyanoacrylate and a non-absorbable or slower absorbing cyanoacrylate are used, the absorption rate can be selected by proper selection of the desired monomer materials, and their relative mixing proportions, and optionally further by proper selection of a desired initiator or accelerator.

20 In preferred embodiments, the present invention provides for the use of quaternary amine polymerization initiators or accelerators such as quaternary amines having the formula



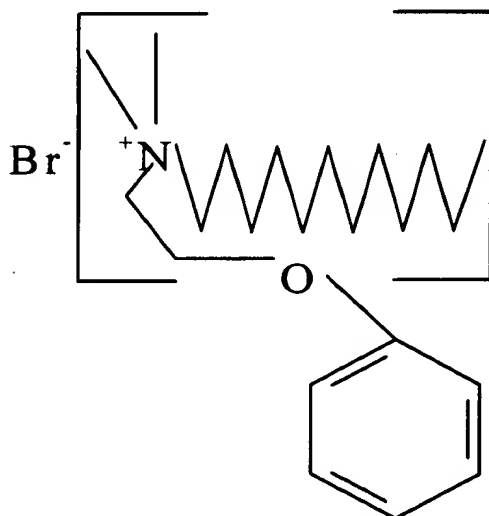
wherein R₄, R₅, R₆ and R₇ are each independently H or a substituted or unsubstituted straight, branched or cyclic alkyl group; a substituted or unsubstituted aromatic ring; a
 30 substituted or unsubstituted aralkyl group; or a substituted or unsubstituted alkyl or aromatic group which may include one or more hetero atom functionalities such as oxygen, sulfur, nitrogen, etc.; and X⁻ is an anion such as a halide, for example chloride, bromide, or fluoride, or hydroxyl. In preferred embodiments, at least one of R₄, R₅, R₆ and R₇ includes an aromatic group and/or a hetero atom functionality such as an ether or
 35 ester linkage or corresponding linkages where the hetero atom is sulfur or nitrogen.

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Preferred quaternary amine initiators are selected from the group consisting of domiphen bromide, butyrylcholine chloride, benzalkonium bromide and acetyl choline chloride.

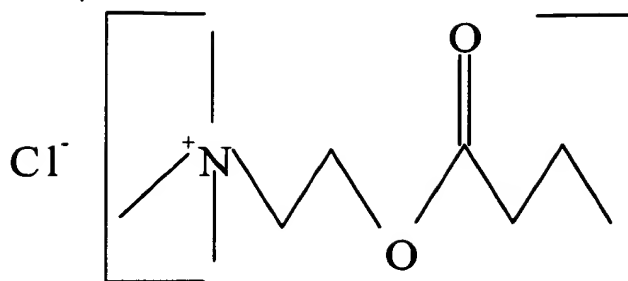
5 Benzalkonium halides, such as benzalkonium chloride, are particularly preferred in embodiments. When used, the benzalkonium halide can be benzalkonium halide in its unpurified state, which comprises a mixture of varying chain-length compounds, or it can be any suitable purified compound including those having a chain length of from about 12 to about 18 carbon atoms, including but not limited to C₁₂, C₁₃, C₁₄, C₁₅, C₁₆, C₁₇, and C₁₈ compounds.

10 Domiphen bromide is preferred in other embodiments. Domiphen bromide may be represented by the following formula:



Butyrylcholine chloride may be represented by the following formula:

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Initiators or accelerators, such as quaternary amines mentioned above, are preferably used in the present invention, but other initiators or accelerators may also be selected by one of ordinary skill in the art without undue experimentation. Such suitable

5 initiators or accelerators may include, but are not limited to, detergent compositions; surfactants: e.g., nonionic surfactants such as polysorbate 20 (e.g., Tween 20TM from ICI Americas), polysorbate 80 (e.g., Tween 80TM from ICI Americas) and poloxamers, cationic surfactants such as tetrabutylammonium bromide, anionic surfactants such as sodium tetradecyl sulfate, and amphoteric or zwitterionic surfactants such as

10 dodecyldimethyl(3-sulfopropyl)ammonium hydroxide, inner salt; amines, imines and amides, such as imidazole, tryptamine, urea, arginine and povidine; phosphines, phosphites and phosphonium salts, such as triphenylphosphine and triethyl phosphite; alcohols such as ethylene glycol, methyl gallate, ascorbic acid, tannins and tannic acid; inorganic bases and salts, such as sodium bisulfite, magnesium hydroxide, calcium

15 sulfate and sodium silicate; sulfur compounds such as thiourea and polysulfides; polymeric cyclic ethers such as monensin, nonactin, crown ethers, calixarenes and polymeric epoxides; cyclic and acyclic carbonates, such as diethyl carbonate; phase transfer catalysts such as Aliquat 336; organometallics such as cobalt naphthenate and manganese acetylacetonate; and radical initiators or accelerators and radicals, such as

20 di-t-butyl peroxide and azobisisobutyronitrile.

In embodiments, mixtures of two or more, such as three, four, or more, initiators or accelerators can be used. A combination of multiple initiators or accelerators may be beneficial, for example, to tailor the initiator of the polymerizable monomer species. For example, where a blend of monomers is used, a blend of initiators may provide

25 superior results to a single initiator. For example, the blend of initiators or accelerators

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process may be conducted numerous times, depending on the size of the wound and the amount of adhesive applied in each application.

The monomeric composition may be packaged in any type of suitable container fabricated from materials including, but not limited to, glass, plastic, metal packages, and film-formed packages. Suitable containers preferably include those into which the compositions may be dispensed and sterilized without unacceptable damage to, or degradation of, the container or the components of the monomer composition. Post-halogenated, such as fluorinated, polymeric barrier layers on at least the monomer-contacting surfaces of the container provide a superior shelf-life for monomer compositions, as disclosed in U.S. Patent Application No. 09/430,289, filed October 29, 1999, the entire disclosure of which is hereby incorporated by reference. Glass is especially preferred when sterilization is achieved with dry heat because of the lack of stability of many plastics at temperatures used for dry heat sterilization. Examples of types of containers include, but are not limited to, ampoules, vials, syringes, pipettes, and the like.

The present invention also provides a saleable kit for delivering an absorbable cyanoacrylate adhesive, or a combination cyanoacrylate adhesive having two different monomers each having different absorption rates, to tissue. In one embodiment, the kit comprises a saleable package comprising a first container that contains at least one alkyl ester cyanoacrylate monomer; and a polymerization initiator or accelerator, wherein the polymerization initiator or accelerator is a quaternary amine. The kit may comprise a second container containing the quaternary amine as described herein. Or, the first container could have the initiator or accelerator in or on it as long as the initiator or accelerator is not in contact with the monomer prior to the desired use.

In other embodiments, the present invention also provides a saleable kit for delivering a combination cyanoacrylate adhesive having two different monomers each having different absorption rates, to tissue. The kit comprises a saleable package comprising a first container that contains a monomer composition comprising a mixture of a non-absorbable monomer species and an absorbable monomer species, or a mixture of a monomer species with a slow absorption/degradation rate and a monomer species with a fast absorption/degradation rate. If desired or necessary, the kit can also include a polymerization initiator or accelerator, wherein the polymerization initiator or accelerator is an initiator or accelerator for at least one of the monomer species and can be, for example, a quaternary amine. The kit can also

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include one or more other additives, including such additives as are described in detail below. When present, each of the additives can independently be either packaged separately from or in combination with the other additives or the monomer composition. As desired, the different monomer species can be packaged separately or together in suitable containers. If packaged separately, the kit provides the user the option of tailoring the absorption or degradation rate by suitably selecting a mixing ratio for the monomer species. The kit may comprise a second container containing a suitable initiator or cross-linking agent, such as a quaternary amine as described herein. Or, the first container could have the optional initiator or accelerator in or on it as long as the initiator or accelerator is not in contact with the monomer prior to the desired use.

The initiator or accelerator is selected so that it functions in conjunction with the co-packaged polymerizable monomer composition to initiate polymerization of at least one of, and preferably at least all of, the monomer species or to modify (e.g., accelerate) the rate of polymerization for the monomers to form a polymeric adhesive. The proper combination of initiator or accelerator and polymerizable monomer can be determined by one of ordinary skill in the art without undue experimentation in light of the present disclosure.

In each of the above embodiments, the kit may also include a suitable applicator, such as a brush, swab, sponge or the like, to assist in applying the composition to living tissue. If desired, the quaternary amine or other initiator and/or other additives can be located in or on the applicator.

The kit is also preferably sterilized; however, the containers and components may be sterilized separately or together. Preferably, kits and the kit components (including compositions) of the present invention have a sterility level in the range of 10^{-3} to 10^{-6} Sterility Assurance Level (SAL) and are sterile for surgical purposes. Various designs of such kits are disclosed, for example, in U.S. Patent Application No. 09/385,030, filed August 30, 1999, the entire disclosure of which is herein incorporated by reference. The sterilization may be accomplished by techniques known to the skilled artisan, and is preferably accomplished by methods including, but not limited to, chemical, physical, and irradiation methods. Examples of physical methods include, but are not limited to, sterile fill, filtration, sterilization by heat (dry or moist) and retort canning. Examples of irradiation methods include, but are not limited to, gamma irradiation, electron beam irradiation, and microwave irradiation. Preferred methods are dry and moist heat sterilization and electron beam irradiation. In embodiments where a

09/19877-08001

composition is to be used for medical applications, the sterilized composition should show low levels of toxicity to living tissue during its useable life.

In embodiments of the present invention, any suitable applicator may be used to apply the adhesive composition to a substrate. For example, the applicator may include an applicator body, which is formed generally in the shape of a tube having a closed end, an open end, and a hollow interior lumen, which holds a crushable or frangible ampoule. The applicator and its related packaging may be designed as a single-use applicator or as a multi-use applicator. Suitable multi-use applicators are disclosed, for example, in U.S. Patent Application No. 09/385,030, filed August 30, 1999, the entire disclosure of which is incorporated herein by reference.

In embodiments of the invention, the applicator may comprise elements other than an applicator body and an ampoule. For example, an applicator tip may be provided on the open end of the applicator. The applicator tip material may be porous, absorbent, or adsorbent in nature to enhance and facilitate application of the composition within the ampoule. Suitable designs for applicators and applicator tips that may be used according to the present invention are disclosed in, for example, U.S. Patent No. 5,928,611 to Leung and U.S. Patent Applications Nos. 09/069,979, filed April 30, 1998, 09/069,875, filed April 30, 1998, 09/479,059, filed January 7, 2000, and 09/479,060, filed January 7, 2000, the entire disclosures of which are incorporated herein by reference.

In embodiments of the present invention, an applicator may contain the initiator or accelerator on a surface portion of the applicator or applicator tip, or on the entire surface of the applicator tip, including the interior and the exterior of the tip. When the initiator or accelerator is contained in or on an applicator tip, the initiator or accelerator may be applied to the surface of the applicator tip or may be impregnated or incorporated into the matrix or internal portions of the applicator tip. Additionally, the initiator or accelerator may be incorporated into the applicator tip, for example, during the fabrication of the tip.

In other embodiments, the initiator or accelerator may be coated on an interior surface of the applicator body and/or on an exterior surface of an ampoule or other container disposed within the applicator body, may be placed in the applicator body in the form of a second frangible vial or ampoule and/or may be otherwise contained within the applicator body, so long as a non-contacting relationship between the

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polymerizable monomer composition and the initiator or accelerator is maintained until use of the adhesive.

Various designs of applicators and methods for incorporating the initiator or accelerator into the applicator are disclosed in U.S. Patent No. 5,928,611 to Leung and
5 U.S. Patent Applications Nos. 09/069,979, filed April 30, 1998, 09/069,875, filed April 30, 1998, 09/145,200, filed September 1, 1998, and 09/479,059 and 09/479,060, both filed January 7, 2000, the entire disclosures of which are incorporated herein by reference.

In embodiments, the polymerizable compositions according to the present
10 invention can further comprise one or more suitable or desirable additives. When incorporated into the composition or used with the composition, it is preferred although not required that the additive or additives also be absorbable. Preferably, the additives have an absorption rate that is about comparable to the absorption rate of the resultant polymer material, although slower or faster absorption rates can be used, as
15 desired.

The polymerizable compositions useful in the present invention may also further contain one or more preservatives, for prolonging the storage life of the composition. Suitable preservatives, and methods for selecting them and incorporating them into adhesive compositions, are disclosed in U.S. Patent Application No.
20 09/430,180, the entire disclosure of which is incorporated herein by reference.

Monomer compositions of the invention may also include a heat dissipating agent. Heat dissipating agents include liquids or solids that may be soluble or insoluble in the monomer. The liquids may be volatile and may evaporate during polymerization, thereby releasing heat from the composition. Suitable heat dissipating
25 agents may be found in U.S. Patent No. 6,010,714 to Leung et al., the entire disclosure of which is incorporated herein.

The composition or solution of the present invention may optionally include at least one plasticizing agent that assists in imparting flexibility to the polymer formed from the monomer. The plasticizing agent preferably contains little or no moisture and
30 should not significantly affect the stability or polymerization of the monomer. Examples of suitable plasticizers include but are not limited to tributyl citrate, acetyl tri-n-butyl citrate (ATBC), polydimethylsiloxane, hexadimethylsilazane and others as listed in U.S. Patent Application Serial No. 09/471,392 filed December 23, 1999, the disclosure of which is incorporated in its entirety by reference herein.

09/19877-080204
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The composition or solution of the present invention may optionally also include thickeners. Suitable thickeners include those listed in U.S. Patent Application Serial No. 09/472,392 filed December 23, 1999, the disclosure of which is incorporated by reference herein in its entirety.

5 The composition or solution of the present invention may also optionally include at least one thixotropic agent. Examples of suitable thixotropic agents and thickeners are disclosed in, for example, U.S. Patent No. 4,720,513, and U.S. Patent Application Serial No. 09/374,207 filed August 12, 1999, the disclosures of which are hereby incorporated in their entireties by reference herein.

10 The composition or solution of the present invention may optionally also include one or more stabilizers, preferably both at least one anionic vapor phase stabilizer and at least one anionic liquid phase stabilizer. These stabilizing agents may inhibit premature polymerization. Suitable stabilizers may include those listed in U.S. Patent Application Serial No. 09/471,392 filed on December 23, 1999, the disclosure
15 of which is incorporated by reference herein in its entirety. Other stabilizing agents, such as free radical stabilizing agents, can also be included as desired.

Compositions or solutions of the present invention may also include at least one biocompatible agent effective to reduce active formaldehyde concentration levels produced during *in vivo* biodegradation of the polymer (also referred to herein as
20 "formaldehyde concentration reducing agents"). Preferably, this component is a formaldehyde scavenger compound. Examples of formaldehyde scavenger compounds useful in this invention include sulfites; bisulfites; mixtures of sulfites and bisulfites, etc. Additional examples of formaldehyde scavenger compounds useful in this invention and methods for their implementation can be found in U.S. Patents Nos. 5,328,687,
25 5,514,371, 5,514,372, 5,575,997, 5,582,834 and 5,624,669, all to Leung et al., which are hereby incorporated herein by reference in their entireties.

The compositions of the present invention may also include pH modifiers to control the rate of degradation of the resulting polymer, as disclosed in U.S. Patent Application No. 08/714,288, filed September 18, 1996, the entire disclosure of which is
30 hereby incorporated by reference herein in its entirety.

To improve the cohesive strength of the compositions or solutions of this invention, difunctional monomeric cross-linking agents may be added to monomer compositions of this invention. Such crosslinking agents are known. U.S. Patent

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No. 3,940,362 to Overhults, which is hereby incorporated herein in its entirety by reference, discloses exemplary cross-linking agents.

The compositions or solutions of this invention may further contain fibrous reinforcement and colorants such as dyes, pigments, and pigment dyes. Examples of suitable fibrous reinforcement include PGA microfibrils, collagen microfibrils, and others as described in U.S. Patent Application Serial No. 09/471,392 filed on December 23, 1999, the disclosure of which is incorporated by reference herein in its entirety.

Other modifications to compositions of the present invention are exemplified by U.S. Patents Nos. 5,624,669; 5,582,834; 5,575,997; 5,514,371; 5,514,372; and 5,259,835; and U.S. Patent Application No. 08/714,288, the disclosures of all of which are hereby incorporated in their entirety by reference.

Although not limited to any particular formulation, a particular composition suitable for use in the present invention comprises a blend of butyl lactoyl cyanoacrylate (BLCA) and octyl cyanoacrylate (OCA). Suitable blends preferably range from about 25:75 to about 40:60 (weight ratio BLCA:OCA). The composition also preferably includes a suitable stabilizer system, such as one comprising specified amounts of sulfuric acid (such as about 25 to about 100 ppm of sulfuric acid, preferably about 20 ppm), sulfur dioxide (such as about 1 to about 50 ppm, preferably about 10 to about 12 ppm), hydroquinone (such as about 100 to about 2000 ppm, preferably about 960 to about 1200 ppm), p-methoxyphenol (such as about 10 to about 200 ppm, preferably about 96 to about 120 ppm), and butylated hydroxyanisole (such as about 100 to about 10,000 ppm, preferably about 500 to about 800 ppm). The composition can include additional materials, such as a colorant such as D & C violet #2 (such as 20 to about 2000 ppm, preferably about 35 to 100 ppm) and the like. Suitable initiators can include, for example, domiphen bromide or benzalkonium chloride, in amounts ranging from about 100 to about 15,000 ppm.

EXAMPLES

The present invention will be further understood by reference to the following non-limiting examples.

Example 1:

70 μ l of butyl lactoyl cyanoacrylate are mixed with 2.5 μ moles of domiphen bromide as the monomer is passed through a porous applicator tip. The resulting mixture sets in approximately 40 seconds. In these Examples, "setting time" is measured as the time when the material reaches its maximum exotherm.

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Example 2:

36 μ l of butyl lactoyl cyanoacrylate are mixed with 0.625 μ moles of butyrylcholine chloride as the monomer is passed through a porous applicator tip. The resulting mixture sets in approximately 60 seconds.

5 Example 3:

A polymer is formed from the initiation of butyl lactoyl cyanoacrylate monomer with domiphen bromide in situ on a polypropylene mesh and placed in a phosphate buffer at 39°C. Samples are rinsed, dried and weighed, and the degradation results of the polymer are shown in the table below, wherein Mn is the number
10 average molecular weight of the sample.

Time (days)	0	28	56	84	112	140
Mass loss (%)	0	8	18	31	45	60
Mn x 1,000	84	12	6.2	3.1	1.9	1.3

A polymer is formed from the initiation of butyl lactoyl cyanoacrylate monomer with azobisisobutyronitrile in situ on a polypropylene mesh and placed in a
15 phosphate buffer at 39°C. Samples are rinsed, dried and weighed, and the degradation results of the polymer are shown in the table below, wherein Mn is the number average molecular weight of the sample.

Time (days)	0	28	56	98	112	140
Mass loss (%)	0	3	6	9	10	12
Mn x 1,000	28	23	23	21	—	20

Example 4:-

20 An absorbable adhesive polymer is formulated by the combination of:

Butyl lactoyl cyanoacrylate monomer	98.2600% (by weight);
Domiphen bromide	1.7300% (by weight);
H ₂ SO ₄	0.0025% (by weight); and
Butylated hydroxyanisole	0.0075% (by weight).

25 Example 5:

Various monomeric adhesive compositions are formulated using varying amounts of butyl lactoyl cyanoacrylate (BLCA) and 2-octyl alpha-cyanoacrylate

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(2OCA). The compositions as formulated also include about 20 ppm sulfuric acid, 0 to 20 ppm sulfur dioxide, 0 to 2000 ppm hydroquinone, 0 to 180 ppm p-methoxyphenol, and 0 to 2000 ppm butylated hydroxyanisole. The mixing ratios of the monomers are set forth in the following Table. The compositions are initiated with domiphen bromide and applied to a surface, and the setting time of the compositions are measured. The setting time results are also set forth in the following Table.

Sample	wt% BLCA	wt% 2OCA	Setting Time (s)
A	0	100	92
B	25	75	60
C	50	50	49
D	75	25	45
E	100	0	42

Example 6:

The same compositions as used in Example 5 are tested *in vitro* for their absorption/degradation rates. As in Example 5, the compositions are formulated using varying amounts of butyl lactoyl cyanoacrylate (BLCA) and 2-octyl alpha-cyanoacrylate (2OCA). The mixing ratios of the monomers are set forth in the following Table.

Samples for *in vitro* degradation testing are prepared by initiating a quantity of the respective monomer composition and expressing it onto a pre-weighed polypropylene mesh having a thickness of approximately 0.19 mm and cut to dimensions of approximately 10 mm x 35 mm. The mesh is sandwiched between two surfaces of ultra high molecular weight polyethylene, which are separated by 0.203 mm thick stainless steel shims. After curing, the samples are removed from the mold and excess polymerized material is trimmed away. A portion of the trimmed away material is used for determining the starting molecular weight of each sample.

The samples are placed into sterilized extraction thimbles to minimize contact with the polymer material. The samples are then placed in sterile glass vials and filled with 21 ml of Dulbecco's phosphate buffered saline (PBS) with antibiotic/antimycotin added. The vials are placed in a water bath at 39°C. The PBS solution is exchanged weekly.

At intervals of 7 and 13 days post-polymerization, the formed polymer is tested to determine the absorption/degradation of the polymer. The

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absorption/degradation is measured by determining the change in mass% of the formed polymer. The testing is conducted by removing the sample from the buffer solution and rinsing them three times with sterile water. The samples are dried for 24 hours in vacuo before re-weighing. The measurements are also set forth in the

5 following Table.

Sample	wt% BLCA	wt% 2OCA	Mass% Change	
			7 days	13 days
A	0	100	-0.4	-0.9
B	25	75	-1.4	-2.1
C	50	50	-2.5	-3.4
D	75	25	-3.6	-5.4
E	100	0	-4.8	-7.8

10 While the invention has been described with reference to preferred embodiments, the invention is not limited to the specific examples given, and other embodiments and modifications can be made by those skilled in the art without departing from the spirit and scope of the invention.

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